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PCT Patent Application No. PCT/EP2004/011860
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New Patent Claims

1. A polypeptide comprising the amino acid sequence SEQ ID NO: 2, 4 or 6 whereby in the polypeptide comprising the amino acid sequence SEQ ID NO: 2, the tyrosine residue at position 88 and/ or the tyrosine residue at position 89 in SEQ ID NO: 2 is/ are phosphorylated, or
whereby in the polypeptide comprising the amino acid sequence SEQ ID NO: 4, the tyrosine residue at position 77 in SEQ ID NO 4 is phosphorylated, or
whereby in the polypeptide comprising the amino acid sequence SEQ ID NO: 6, the tyrosine residue at position 91 in SEQ ID NO 6 is phosphorylated.

2. A polypeptide according to claim 1 comprising the amino acid sequence SEQ ID NO: 2, whereby the tyrosine residues at position 88 and/ or the tyrosine residue at position 89 in SEQ ID NO: 2 are phosphorylated and whereby the serine residue at position 10 and/or 12 and/or the threonine residue at position 157 and/or the threonine residue at position 187 in SEQ ID NO: 2 are phosphorylated.

3. A peptide fragment with a minimum length of 6 amino acids of a polypeptide comprising the amino acid sequence SEQ ID NO: 2, 4 or 6,
whereby in the peptide fragment of a polypeptide comprising the amino acid sequence SEQ ID NO: 2, the tyrosine residue at position 88 and/ or the tyrosine residue at position 89 in SEQ ID NO: 2 is/ are phosphorylated, or
whereby in the peptide fragment of a polypeptide comprising the amino acid sequence SEQ ID NO: 4, the tyrosine residue at position 77 in SEQ ID NO 4 is phosphorylated, or
whereby in the peptide fragment of a polypeptide comprising the amino acid sequence SEQ ID NO: 6, the tyrosine residue at position 91 in SEQ ID NO 6 is phosphorylated.

4. A peptide fragment according to claim 3 with a minimum length of 10 amino acids, preferably with a minimum length of 15 amino acids.

5. A polypeptide
comprising the amino acid sequence SEQ ID NO: 2, 4 or 6 or
comprising the amino acid residues 1 to 95 of SEQ ID NO: 2 or comprising the amino acid residues 1 to 85 of SEQ ID NO: 4 or comprising the amino acid residues 1 to 100 of SEQ ID NO: 6 or
comprising the amino acid residues 50 to 95 of SEQ ID NO: 2 or comprising the amino acid residues 38 to 85 of SEQ ID NO: 4 or comprising the amino acid residues 50 to 100 of SEQ ID NO: 6
characterized in that in the polypeptide derived from the polypeptide with the amino acid sequence SEQ ID NO: 2, the amino acid residue at position 88 and/or position 89 in SEQ ID NO: 2, or
in the polypeptide derived from the polypeptide with the amino acid sequence SEQ ID NO: 4, the amino acid residue at position 77 in SEQ ID NO: 4 or
in the polypeptide derived from the polypeptide with the amino acid sequence SEQ ID NO: 6, the amino acid residue at position 91 in SEQ ID NO: 6
is a non-phosphorylatable amino acid residue, preferably a phenylalanine residue.

6. A peptide fragment with a minimum length of 6 amino acids of a polypeptide comprising the amino acid sequence SEQ ID NO: 2, 4 or 6, characterized in that in the peptide fragment of a polypeptide comprising the amino acid sequence SEQ ID NO: 2, the peptide fragment comprises at least one of the flanking amino acid residues of the amino acid residue at position 88 or 89 in SEQ ID NO: 2 and the residue at position 88 and/ or the residue at position 89 in SEQ ID NO: 2 is a non-phosphorylatable amino acid residue, preferably a phenylalanine residue, or
in the peptide fragment of a polypeptide comprising the amino acid sequence SEQ ID NO: 4, the peptide fragment comprises at least one of the flanking amino acid residues of the amino acid residue at position 77 in SEQ ID NO: 4 and the residue at position 77 in SEQ ID NO: 4 is a non-phosphorylatable amino acid residue, preferably a phenylalanine residue, or
in the peptide fragment of a polypeptide comprising the amino acid sequence SEQ ID NO: 6, the peptide fragment comprises at least one of the flanking amino acid residues of the amino acid residue at position 91 in SEQ ID NO: 6 and the residue at position 91 in SEQ ID NO: 6 is a non-phosphorylatable amino acid residue, preferably a phenylalanine residue.

7. A variant or peptidomimetics of the polypeptide according to any of the claims 1, 2 or 5 or a variant or peptidomimetics of the peptide fragment according to the claims 3, 4 or 6.

8. A nucleic acid molecule encoding a polypeptide according to claim 5 or a peptide fragment according to claim 6 or a vector comprising a nucleic acid molecule encoding a polypeptide according to claim 5 or a peptide fragment according to claim 6.

9. An isolated antibody which specifically binds to a polypeptide according to any of the claims 1 to 2 or to a peptide fragment according to the claims 3 or 4 and which has less than 10% cross reactivity with the corresponding non-phosphorylated polypeptide or corresponding non-phosphorylated peptide fragment.

10. The antibody of claim 9, wherein the antibody is a monoclonal antibody.

11. The antibody of claim 10 wherein the monoclonal antibody is produced by the hybridoma cell line Mab<p27kip>15 or Mab<p27kip>388.

12. The antibody of claim 9, wherein the antibody is a polyclonal antibody.

13. The hybridoma cell line Mab<p27kip>15 or Mab<p27kip>388 as deposited with the DSMZ.

14. A polypeptide according to claim 1, 2, or 5, a peptide fragment according to claim 3, 4 or 6, a variant or peptidomimetics according to claim 7, a nucleic acid molecule according to claim 8, an antibody according to any of the claims 9 to 12 for use in medicine.

15. A pharmaceutical composition comprising a polypeptide according to claim 1, 2, or 5, a peptide fragment according to claim 3, 4 or 6, a variant or peptidomimetics according to claim 7, a nucleic acid molecule according to claim 8 or an antibody according to any of the claims 9 to 12 and a pharmaceutically acceptable carrier.

16. Use of a polypeptide according to claim 1, 2, or 5, a peptide fragment according to claim 3, 4 or 6, a variant or peptidomimetics according to claim 7, a nucleic acid molecule according to claim 8 or an antibody according to any of the claims 9 to 12 for the preparation of a pharmaceutical composition for the treatment of hyperproliferative disease, preferably cancer.

17. A method for the determination of the amount or presence of a polypeptide according to any of the claims 1 or 2 or a peptide fragment according to any of the claims 3 or 4 in a sample comprising the steps of
    a) providing a sample suspected to contain the polypeptide or the peptide fragment,
    b) incubating the sample in the presence of an antibody according to any of the claims 9 to 12, and
    c) determining the binding product between the polypeptide and the antibody thereby concluding that the polypeptide or peptide fragment is present or thereby deriving the amount of the polypeptide or the peptide fragment.

18. A method of determining whether or not a human cancer cell containing patient sample has potential for tumor progression, the method comprising comparing:
    a) the level of expression a polypeptide according to any of the claims 1 to 2 or a peptide fragment according to claim 3 or 4 in the patient sample, and
    b) the normal level of expression the polypeptide or the peptide fragment in a sample from a control subject not afflicted with cancer,

    and an at least 1.5 fold difference or a less than 0.75 fold difference between the level of expression of the polypeptide or the peptide fragment in the patient sample and the normal level of the polypeptide or the peptide fragment in the sample from a control subject not afflicted with cancer is an indication that the patient sample has potential for tumor progression.

19. A method of selecting a composition for inhibiting the progression of cancer in a patient, the method comprising:
    a) providing a sample comprising cancer cells from the patient;
    b) separately exposing aliquots of the sample in the presence of a plurality of test compositions;
    c) comparing the level of expression of the polypeptide according to any of the claims 1 to 2 or a peptide fragment according to any of the claims 3 or 4 in each of the aliquots; and
    d) selecting one of the test compositions which alters the level of expression of the polypeptide in the aliquot containing that test composition, relative to other test compositions.

20. The method according to any of the claims 18 to 19, wherein the presence or the level of expression of said polypeptide or said peptide fragment is detected using a reagent which specifically binds with said polypeptide or peptide fragment.

21. The method of claim 20, wherein the reagent is selected from the group consisting of an antibody, an antibody derivative, and an antibody fragment.

22. The method according to claim 21 wherein the antibody is an antibody according to any of the claims 9 to 12.

23. The method according to any of the claims 18 to 22 wherein the human cancer cell is a breast cancer cell, a colorectal cancer cell or a leukaemia cell, preferably a Philadelphia chromosome positive leukemia cell, more preferably a chronic myeloid leukaemia cell or an acute lymphoblastic leukemia cell.

24. The method according to any of the claims 18 to 23, wherein the sample is a tissue sample, blood or blood derived cells, primary cell cultures from patients, stool, lymph or a tissue-associated fluid or urine.

25. A method to predict which patients will respond to a tyrosine kinase inhibitor drug in patients with a disorder whose underlying pathology involves the discontrol of a tyrosine kinase comprising:

a) contacting a sample from a patient with an antibody according to any of the claims 9 to 12
b) determining the level of phosphorylated polypeptide bound by the antibody of step a)
c) comparing the level of phosphorylated polypeptide determined in step(b) for the sample with the level of phosphorylated protein in a reference sample, thereby detecting the responsiveness to a tyrosine kinase inhibitor drug in patients with a disorder whose underlying pathology involves the discontrol of a tyrosine kinase.

26. The method according to claim 25 wherein the reference sample is a sample from a patient who responds to the tyrosine kinase inhibitor drug.

27. The method according to any of the claims 25 to 26 wherein the tyrosine kinase inhibitor is imatinib mesylate.

28. The method according to any of the claims 25 to 27 wherein the patients with a disorder whose underlying pathology involves the discontrol of a tyrosine kinase are cancer patients.

29. The method according to claim 28 wherein the cancer patients are Philadelphia chromosome positive leukemia patients preferably, chronic myeloid leukaemia patients or acute lymphoblastic leukemia patients.

30. A kit for the detection or determination of the amount of the polypeptide according to any of the claims 1 to 2 or the peptide fragment according to any of the claims 3 or 4 in a biological sample which comprises:
    (a) an antibody according to any of the claims 9 to 12 and
    (b) a label for qualitatively or quantitatively detecting an immunoconjugate of the antibody and the polypeptide or the peptide fragment.

31. A method of deriving a candidate agent, said method comprising:
    (a) contacting a sample containing cancer cells, with said candidate agent;
    (b) determining the level of expression of the polypeptide according to any of the claims 1 to 2 or a peptide fragment according to any of the claims 3 or 4 in the sample contacted with the candidate agent and determining the level of expression of the polypeptide in a sample not contacted with the candidate agent;
    (c) observing the effect of the candidate agent by comparing the level of expression of the polypeptide or the peptide fragment in the sample contacted with the candidate agent and the level of the polypeptide or the peptide fragment in the sample not contacted with the candidate agent,
    (d) deriving said agent from said observed effect,

    wherein an at least 1.5 fold difference or a less than 0.75 fold difference between the level of expression of the polypeptide or the peptide fragment in the sample contacted with the candidate agent and the level of expression of the polypeptide or the peptide fragment in the sample not contacted with the candidate agent is an indication of an effect of the candidate agent.

32. The method according to claim 31, wherein said candidate agent is a candidate inhibitory agent.

33. The method according to claim 32, wherein said candidate agent is a candidate enhancing agent.

34. Use of an antibody according to any of the claims 9 to 12 for the determination of the amount or presence of a polypeptide according to any of the claims 1 or 2 or a peptide fragment according to any of the claims 3 or 4 in a sample.

35. Use of a polypeptide according to any of the claims 1 to 2 or 5, preferably according to claim 1 or 2, or of a peptide fragments according to any of the claims 3 to 4 or 6, preferably according to claims 3 to 4, for the determination of the potential of a human cancer cell for tumor progression or for the prediction which patients with a disorder whose underlying pathology involves the discontrol of a tyrosine kinase will respond to a tyrosine kinase inhibitor drug.

36. Use of a nucleic acid molecule according to claim 8 for the expression of a polypeptide according to claims 5 or a peptide fragment according to claim 6.

37. Use of a polypeptide according to any of the claims 1 to 2 or 5, preferably according to the claim 1 or 2, or of a peptide fragment according to any of the claims 3 to 4 or 6, preferably according to the claims 3 to 4, as an immunogen to generate or produce antibodies, in particular monoclonal antibodies.

38. A virus particle comprising a nucleic acid molecule or a vector according to claim 8.

39. A mammalian cell comprising a nucleic acid molecule or a vector according to claim 8.

40. A virus particle according to claim 38 or a mammalian cell according to claim 39 for use in medicine.

41. A pharmaceutical composition comprising a virus particle according to claim 38 or a mammalian cell according to claim 39 and a pharmaceutically acceptable carrier.

42. Use of a virus particle according to claim 38 or a mammalian cell according to claim 39 for the preparation of a pharmaceutical composition for the treatment of cancer.